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Co-operative effects in tumorigenicity. The microcystin example.

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Introduction

Cyanobacteria have been implicated in many deaths of livestock, wildlife and human throughout the world.[1] They produce a broad range of biologically active substances including proteinase inhibitors[2], endotoxins (LPS), which are generally present in gram-negative bacteria[3], and a variety of other toxic compounds.[4] These substances are released in the water environment during the senescence of the bloom and can penetrate in the water supply system. Little attention has been paid to possible synergistic interactions between these biologically active substances in tumor promotion and tumor initiation.

With few exceptions[5], the vast majority of experiments used for the human risk assessment of cyanobacteria have been performed using purified microcystins.[6] To evaluate liver injuries such as cirrhosis and hepatocellular carcinoma high doses of pure microcystins have been used.[7] The present paper presents an attempt to verify the possible synergistic effects of different biologically active substances we have tested the toxic effects of lyophilized hepatotoxic cyanobacteria in comparison to the effects produced by the same amounts of purified microcystins.

Materials and methods

The toxicity was estimated by a mouse bioassay and the microcystins isolated and determined as described elsewhere.[8] Acute and sub chronic experiments were performed on Wistar rats and New Zealand rabbits, as described previously.[9] The toxic material was injected intraperitoneallly (*i.p.*).

Results and discussion

In our experiments we have been able to detect precancerosis after application of much lower amount of microcystins in lyophilized cyanobacteria (2 LD_{50} injected during the 5 weeks period). This amount is on average 4 fold lower, than the amount used by other authors in order to produce similar injuries by *i.p.* application of purified microcystins. Since endotoxins (LPS) present in cyanobacteria have a profound effect on detoxification of microcystins by the suppression of glutathione S- transferase activity[10] they may enable the accumulation of microcystins in the liver of exposed organisms (Figure 1).

The persistence of microcystins in liver cells may be responsible for the more pronounced changes in the liver of animals treated with whole cyanobacteria in comparison to the animals treated with pure microcystins (Figure 2).

Experimental data imply that microcystins can no longer be treated merely as tumor promoters since it has been demonstrated that prolonged exposure to microcystins can induce neoplastic nodular formation.[7] Additionally, DNA damages have been observed as a result of exposure to microcystins.[11]

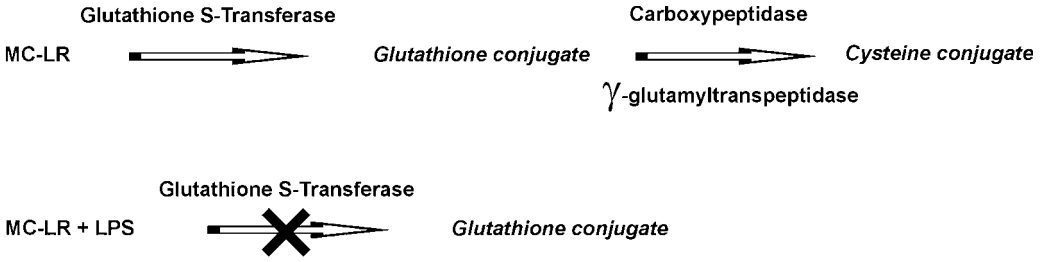

Figure 1. Inhibition of microcystin detoxification in the presence of endotoxin (LPS) as suggested by Pflugmaher and coworkers.

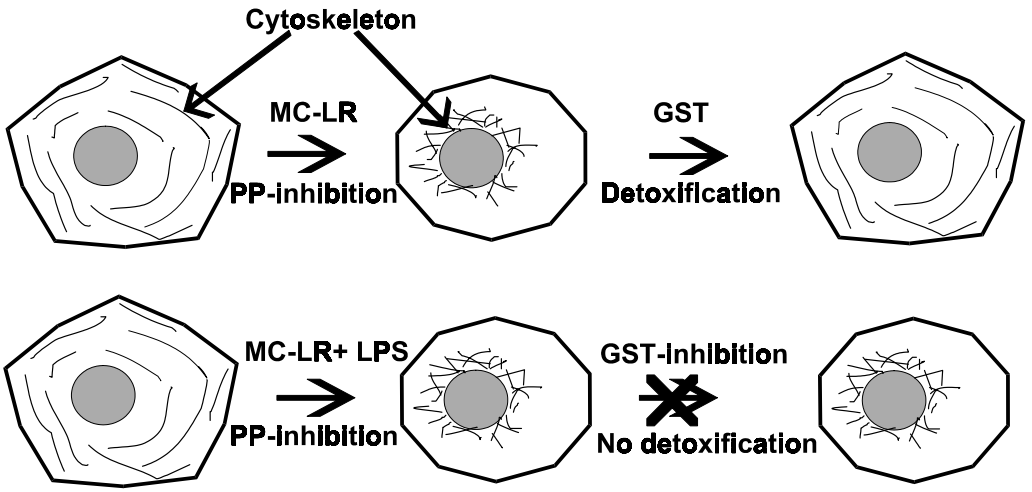

Figure 2. Prolonged action of microcystis on liver cells due to the inhibition of detoxification.

We must be aware that several other toxic or carcinogenic substances found in environmental waters can be dissolved, adsorbed or trapped on the surface of cyanobacteria. Therefore, in our opinion the health risk of cyanobacteria can not be established only on the basis of microcystin contents, meaning that the risk is underestimated.

Conclusion

New experimental data on cyanobacterial toxicity suggest that the extrapolation of the health risk of microcystins from acute and sub chronic experiments performed mainly with purified toxins is not adequate. Other biologically active substances normally present in cyanobacterial blooms can amplify their toxic effects. There are also evidences, that microcystins are able to damage the genetic material of exposed animals and can even induce formation of neoplastic nodular formation. Therefore, at least in our opinion, the health risk of natural cyanobacterial blooms is underestimated.

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